ABCC GRID Promoter TFSite Comparison Page to find shared regulatory elements for co-regulated genes in toxicology

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BACKGROUND

Toxicological studies often yield lists of genes potentially co-regulated based on coordinate expression changes. Three examples demonstrate that new hypotheses and research directions can be proposed by identification of potential transcription factor binding sites shared among a group of genes, the service the web page provides. Use in toxicological dose-response gene expression studies and similar treatment-response experimental paradigms is discussed, including limitations of the application.

WEB TOOL

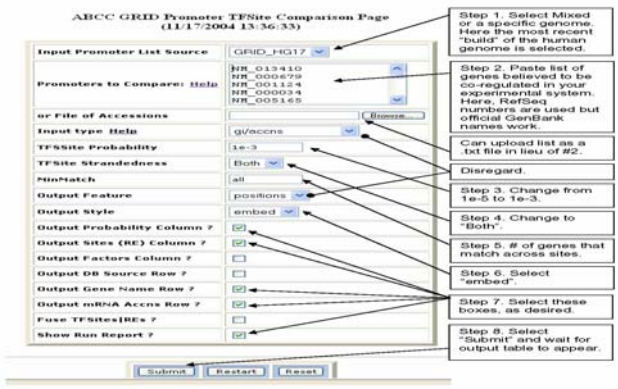


Figure 1. Quick Results Example of Website page for Promoter Analysis. Users can access the website, paste in their favorite gene list and, using the options shown, promptly have a list of potential transcriptional regulatory sites common to the submitted genes.

APPLICATIONS

Table 1. Genes reported to be Hif1α-regulated used for validating Transcription Factor Analysis.

Gene Product	Transcription Factor	UniGene	Name	RefSeq ID
Adenylate kinase 3	HIF-1	Hs.211700	AK3	XM_371832
A1B-Adrenergic receptor	HIF-1	Hs.416813	ADRA1B	NM_000679
Adrenomedullin	HIF-1	Hs.441047	ADM	NM_001124
Aldolase A	HIF-1	Hs.273415	ALDOA	NM_000034
Aldolase C	HIF-1	Hs.155247	ALDOC	NM_005165
Carbonic anhydrase-9	HIF-1	Hs.63287	CA9	NM_001216
Ceruloplasmin	HIF-1	Hs.364013	SLC26A7	NM_052832
Cyclooxygenase-2	HMG I(Y), NF-κB	Hs.196384	PTGS2	NM_000963
Endothelin-1	HIF-1	Hs.511899	EDN1	NM_001955
Enolase-1	HIF-1	Hs.433465	ENO1	NM_001428
Erythropoietin	HIF-1	Hs.2303	EPO	NM_000799
GADD153	Not determined	Hs.135406	CEBPZ	NM_005760
Glucose transporter-1	HIF-1	Hs.169002	SLC2A1	NM_006516
Glucose transporter-3	HIF-1	Hs.419240	SLC2A3	NM_006931
Glyceraldehyde-3-phosphate dehydrogenase	HIF-1	Hs.169476	GAPD	NM_002046
Heme oxygenase-1	AP-1, HIF-1	Hs.202833	HMOX1	NM_002133
Hexokinase-1	HIF-1	Hs.118625	HK1	NM_000188
Hexokinase-2	HIF-1	Hs.406266	HK2	NM_000189
Insulin-like growth factor-2 (IGF-2)	HIF-1	Hs.348109	IGF2	NM_000612
IGF-binding protein-1	HIF-1	Hs.413116	IGFBP1	NM_000596
IGF-binding protein-2	HIF-1	Hs.433326	IGFBP2	NM_000597
IGF-binding protein-3	HIF-1	Hs.450230	IGFBP3	NM_000598
Interleukin-6	NF-IL6	Hs.512234	IL6	NM_000600
Lactate dehydrogenase A	HIF-1	Hs.2795	LDHA	NM_005566
Nitric oxide synthase-2	HIF-1	Hs.193788	NOS2A	NM_000625
NIP3	HIF-1	Hs.79428	BNIP3	NM_004052
Ornithine decarboxylase	Not determined	Hs.443499	ODC1	NM_002539
P21	HIF-1	Hs.370771	CDKN1A	NM_078467
P27	Not determined	Hs.238990	CDKN1B	NM_004064
P35srj	HIF-1	Hs.93597	CDK5R1	NM_003885
Phosphofructokinase L	HIF-1	Hs.368741	PFKL	NM_002626
Phosphoglycerate kinase-1	HIF-1	Hs.79771	PGK1	NM_000291
Plasminogen activator inhibitor-1	HIF-1	Hs.414795	SERPINE1	NM_000602
Prolyl-4-hydroxylase α (I)	HIF-1	Hs.271224	PH-4	NM_177939
Pyruvate kinase M	HIF-1	Hs.196281	PKM2	NM_002654
Tissue factor	EGR-1	Hs.62192	F3	NM_001993
Transferrin	HIF-1	Hs.433923	TF	NM_001063
Transferrin receptor	HIF-1	Hs.180728	TFRC	NM_003234
Transforming growth factor β3	HIF-1	Hs.2026	TGFB3	NM_003239
Triosephosphate isomerase	HIF-1	Hs.512711	TPI1	NM_000365
Tyrosine hydroxylase	AP-1	Hs.435609	TH	NM_000360
Vascular endothelial growth factor (VEGF)	HIF-1	Hs.73793	VEGF	NM_003376
VEGF receptor FLT-1	HIF-1	Hs.347713	FLT1	NM_002019

Table 2. Regulatory elements common within chronosequential gene expression patterns. N.B.: Minus U937 subclone at left; Plus subclone at right. U = up > 2-fold, D = down > 2-fold over the intervals 0-6, 6-24, and 24-48 hrs.

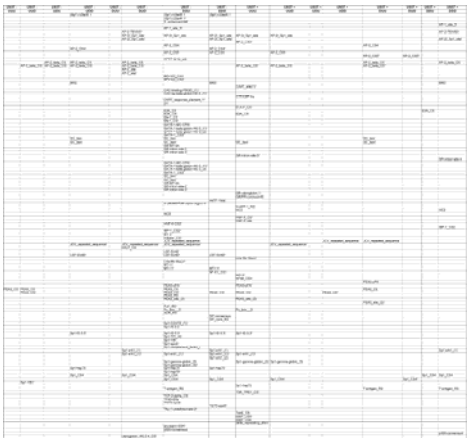
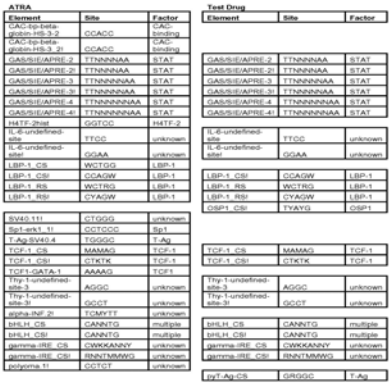


Table 3. Regulatory elements comparing two differentiation agents for genomic response down-regulated at 6 hrs using ABCC GRID Promoter TFSite.Comparison Page website.



For Table 1, Hif1α-regulated genes all exhibited Hif-response elements in their promoter regions except one found only in mice. For Table 2, groups of genes expressed could be compared both between subclones and between temporal patterns. For Table 3, two chemical treatments that induce differentiation through different means exhibit slight variations in regulatory elements reported.

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